describes the use of cysteine to prevent fusion proteins of insulin and insulin derivatives from improper folding until a researcher initiates controlled reductive folding into the correct preproinsulin forms. New claim 78 is similar to claim 54, but depends on claim 23 rather than on claim 48. New claims 79-84 recite the subject matter of unamended claims 35-37 and 65-67, which the Office has not rejected. Applicants submit that these amendments do not introduce new matter or require a further search of the art, and respectfully request their entry.

Rejection of Claims 23-34, 40-46, 48-64, and 70-77 under 35 U.S.C. § 103(a)

The Office maintains the rejection of claims 23-34, 40-46, 48-64, and 70-77, alleging that they are obvious over Flaa et al. ("Flaa"; WO 96/27661), Mikura et al. ("Mikura"; EP 158487), Ahmad et al. ("Ahmad"; *J. American Oil Chemists' Soc.*, 60(4): 837-40), and Santha et al. ("Santha"; *Indian J. Animal Sci.*, 49(1): 37-41). (Office Action at pages 2-3.) Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness must meet several essential criteria. First, the prior art references must teach or suggest all of the claim limitations. M.P.E.P. § 2142. Second, there must be a suggestion or motivation to modify the references or to combine their teachings. *Id.* Third, there must be a reasonable expectation of success in performing that modification or combination. *Id.* Finally, both the motivation to combine the references and the reasonable expectation of success must be found in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, and not in the applicant's disclosure. *Id.*

Moreover, the mere fact that references *can* be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430

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1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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(Fed. Cir. 1990). The modification or combination must be *desirable*, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000). Thus, without an objective teaching, incentive, or suggestion in the prior art to combine the references in the manner that the applicant claims, there is no motivation to combine references. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000); *In re Napier*, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995).

Applicants first submit that none of Flaa, Mikura, Ahmad, or Santha teach or suggest adding cysteine to a protein in aqueous solution in an amount effective in "preventing chemical modification of SH groups on the protein during a period of greater than 24 hours," as required by claim 48. Nor do they teach or suggest adding cysteine to achieve this effect such that the "effective concentration does not decrease by more than about 7%," as required by claim 23.

Applicants also submit that the Office has failed to show that one of ordinary skill in the art would be motivated to combine the teachings of Flaa, Mikura, Ahmad, and Santha in order to obtain Applicants' claimed invention. There is no objective teaching, suggestion, or incentive to combine them. In addition, there is no reasonable expectation that the claimed invention would be obtained successfully if the teachings of the four references were combined. Thus, the Office has not established a *prima facie* case of obviousness.

Flaa discusses a "non-human serum derived control and/or calibrator matrix" that may be useful for stabilizing troponin, for example. (Flaa at page 7, lines 9-17.) A "reducing agent" is one of several different types of ingredients added to the matrix, including a buffer, "stabilizing protein," "blocking agent," "chelating agent," salt, and

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1300 I Street, NW
Washington, DC 20005
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protease inhibitor. (*Id.* at pages 7-11.) Cysteine is not among the listed reducing agents. (*Id.* at page 11, lines 1-7.) The disclosure in Flaa, as a whole, does not focus on any particular component of the mixture as being effective to impart stabilization to troponin or any other protein, and is entirely silent as to any modification of SH groups. (Flaa at pages 7-11.) Nor does Flaa postulate how its mixture of ingredients may function to stabilize proteins. Therefore, Flaa does not teach that reducing agents are "effective to reduce the temporal decrease in the effective concentration by preventing chemical modification of SH groups" of any protein.

Moreover, Flaa's stabilizing solution does not achieve the level of delay in the temporal decrease in the protein's effective concentration throughout the 24 hour to two-month range of time that Applicants claim. For example, none of the figures shown in Flaa depicts solutions that are more than about 80-90% stable during this time period. In Figure 1, the refrigerated solution falls to 90% stability within the first day of storage, and then to about 80% on the second day. In Figure 2, the protein is never more than 80% stable. Figures 3, 5, and 6 show similar results. While Figure 4 depicts a few data points indicating stability greater than 90%, the results fluctuate considerably, suggesting that there is a large amount of error in the data. Thus, Flaa does not teach an amount of any reducing agent that would be effective in preventing a decrease in the effective concentration of a protein by more than 7%, as described in claim 23.

Mikura focuses upon lyophilizing IL-2 solutions containing glutathione or ascorbate reducing agents, as well as other ingredients. (*See* Mikura at Examples 1-12.) Because of Mikura's focus upon lyophilization, the results presented in Examples 1-12 are not relevant to the stability of proteins in liquid solutions, as Applicants claim.

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For example, one of ordinary skill in the art would recognize that the reason why some proteins are lyophilized is because they cannot be effectively stabilized in aqueous solution. Mikura also lists a large genus of possible reducing agents used over a 400-fold concentration range, while all of its working examples recite only glutathione or ascorbate. (Mikura at page 3, lines 2-12.) Finally, Mikura is silent about modification of SH groups.

As a whole, the Flaa and Mikura references do not recite several of the elements of Applicants' claims. They do not disclose cysteine, are silent as to whether the solutions they disclose can prevent modification of SH groups, and do not teach reducing agents "effective to delay the temporal decrease in the effective concentration" of a protein in an aqueous solution such that the decrease in effective concentration is no more than about 7%.

The Office cites Ahmad and Santha for a teaching that cysteine is an antioxidant. These references do not teach proteins in aqueous solutions, however. Instead, they pertain to preserving food oils. Therefore, they do not remedy Flaa and Mikura's failure to teach the requirements of claim 23 and 48: that the additive be "effective to delay the temporal decrease in the effective concentration" of a protein by no more than about 7%," "by preventing chemical modification of SH groups." At best, these teachings are missing from the four publications, one of ordinary skill in the art would not reasonably expect to be able to combine these references to achieve the claimed process, and would, therefore, not be motivated to do so.

For these reasons, claims 23-34, 40-46, 48-64, and 70-77 are unobvious, and Applicants respectfully request the withdrawal of this rejection.

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HENDERSON
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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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Rejection of Claims 23-24, 33, 40-42, 48-54, and 63 under 35 U.S.C. § 102(b)

The Office rejects claims 23-24, 33, 40-42, 48-54, and 63, alleging that they are anticipated by Qi et al. ("Qi"; *PDA J. Pharm. Sci. Tech.*, 49(6): 289-92 (1995)). (Office Action at pages 3-4.) Applicants respectfully traverse this rejection.

Applicants note that for a reference to anticipate a claim, it must disclose each and every element of that claim either expressly or inherently, and in as complete detail as is recited in the claim. M.P.E.P. § 2131. Qi does not anticipate any of claims 23-24, 33, 40-42, 48-54, and 63 because it does not teach, either inherently or expressly, a solution containing an amount of cysteine "effective to delay the temporal decrease in the effective concentration of a protein by preventing chemical modification of SH groups."

Instead, Qi and coauthors added 4 to 8 mM cysteine to the hormone insulinotropin in order to prevent oxidative degradation of a tryptophan residue that is apparently accelerated by the presence of dextran beads. (Qi at Introduction and at pages 292-3.) Insulinotropin, also known as glucagon-like peptide I (7-37), is a 31-amino acid peptide with no SH groups. (See Kieffer & Habener at page 883; Exhibit A.) According to Figures 7 and 8 of Qi, at page 292, very low concentrations (0.1% or 4-8 mM) of free amino acids, such as tryptophan, histidine, and cysteine were useful in preventing the degradation of the tryptophan residue on the peptide, but reducing agents such as ascorbic acid were not able to stabilize the peptide. (Qi at Figure 7.) Thus, Qi does not teach or suggest preventing the modification of SH groups on a protein or the amounts of cysteine as claimed. Applicants, therefore, respectfully request the withdrawal of this rejection.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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Rejection of Claims 25-32, 43-47, 55-62, and 73-77 under 35 U.S.C. § 103(a)

The Office also asserts that claims 25-32, 43-47, 55-62, and 73-77 are allegedly obvious over Qi. (Office Action at page 4.) Applicants respectfully traverse this rejection.

Applicants first reiterate that in order for a reference to render a claim obvious under § 103, it must teach or suggest all of the elements of that claim. However, as described in the preceding section, Qi does not teach or suggest a solution containing an amount of cysteine "effective to delay the temporal decrease in the effective concentration of a protein by preventing the chemical modification of SH groups," as required by all of claims 25-32, 43-47, 55-62, and 73-77. Moreover, because Qi is completely silent as to the modification of SH groups, Qi provides no objective teaching or incentive to modify its teachings to obtain the claimed invention. Therefore, the Office has failed to provide a *prima facie* case of obviousness, and Applicants request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

FINNEGAN
HENDERSON
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DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: May 9, 2003

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX TO AMENDMENT OF MAY 9, 2003

Version Sh wing Changes Marked-Up

Amendments to the Claims:

23. (Amended) A process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by preventing chemical modification of SH groups on the protein during storage, wherein the effective concentration does not decrease by more than about 7%.

48. (Amended) A process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease in the effective concentration of the protein by preventing chemical modification of SH groups on the protein during a period of greater than 24 hours.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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